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Adjuvanted Quadrivalent Influenza vaccine (aQIV) in young children

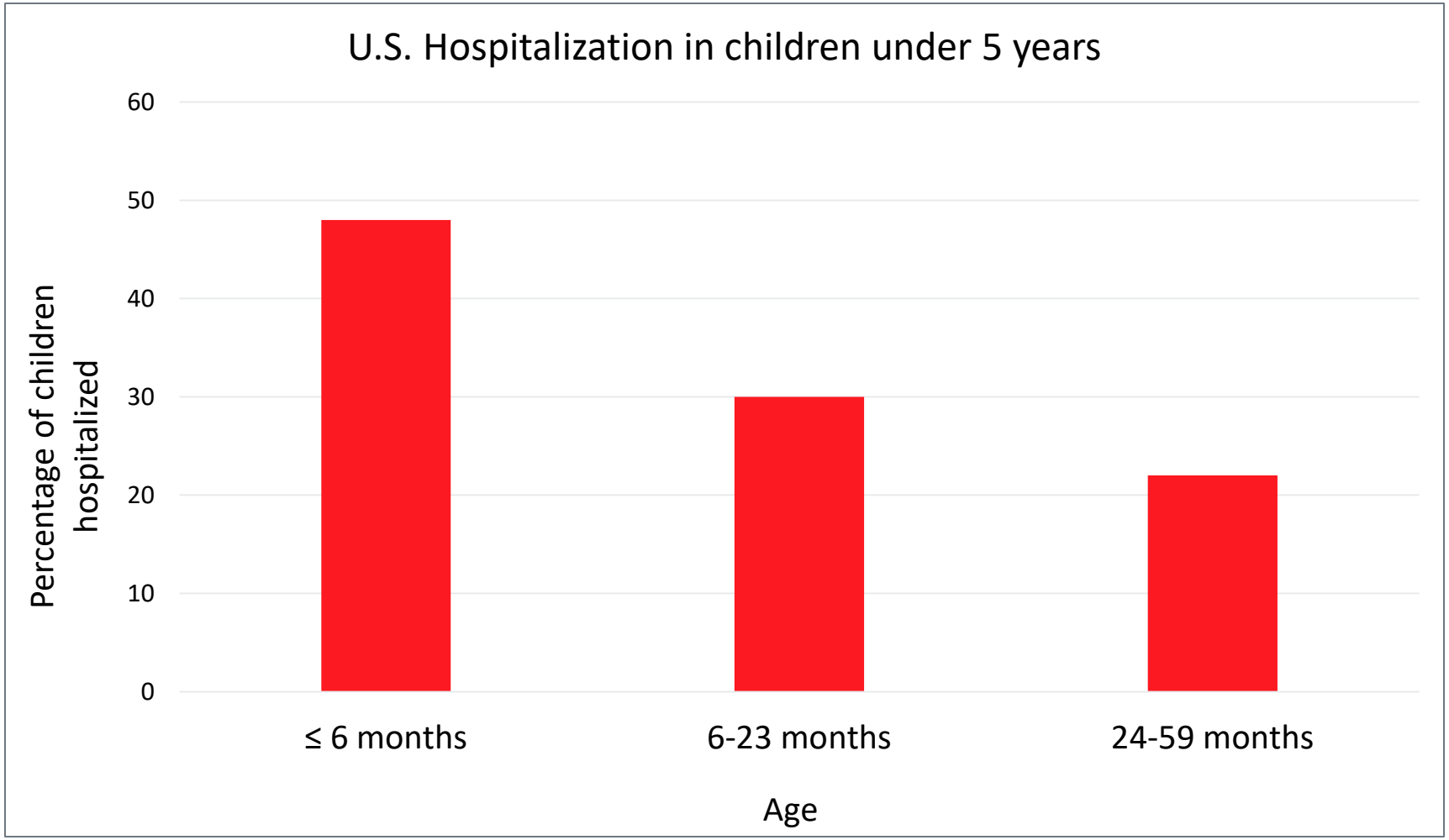
Gregg C. Sylvester, MD, MPH
Medical Affairs

- Burden of Disease

- Adjuvanted QIV (aQIV) Pivotal Results in young children
  - Study Design
  - Demographics/Characteristics
  - Results
    - Efficacy
    - Immunogenicity
    - Safety
  - Summary

aTIV=MF59-adjuvanted trivalent inactivated influenza vaccine
aQIV=MF59-adjuvanted quadrivalent inactivated influenza vaccine

Hospitalization for Influenza in Children Over Two Influenza Seasons (2002–2004)



Poehling KA, et al. N Engl J Med. 2006;355:31–40

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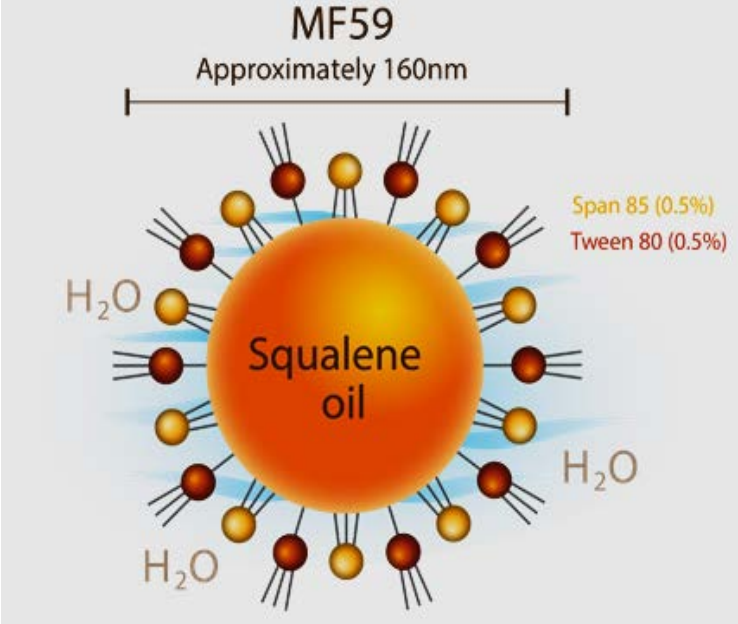
Oil-in-Water Adjuvant: MF59® *Composition*

- First approved in 1997 in FLUAD
- MF59 is an oil-in-water emulsion composed of squalene
- Squalene
  - Biodegradable and biocompatible oil
  - Intermediate precursor in the cholesterol biosynthetic pathway
  - Synthesized in the liver (>1 g/day) and derived from dietary sources (50 mg–200 mg/day)



O'Hagan DT, et al. *Expert Rev Vaccines.* 2013;12:13-30.

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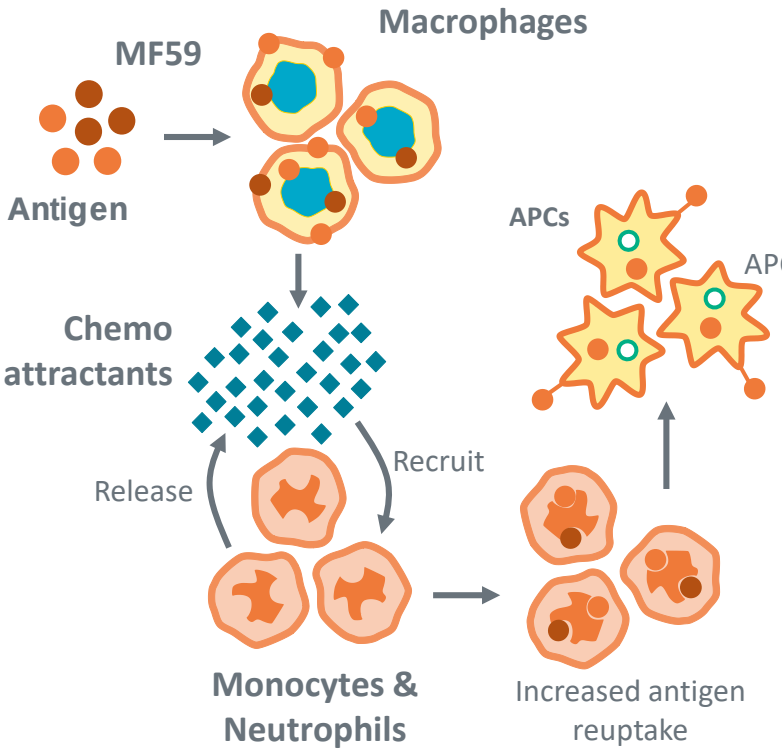
MF59: *Mode of Action at Injection Site*

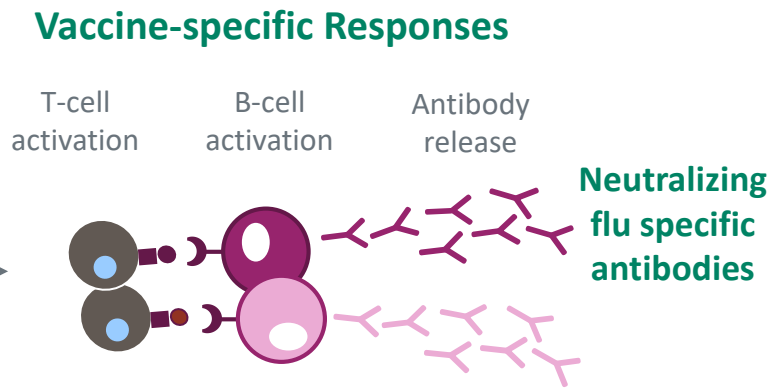
Injection Site

1. MF59 recruits immune cells[1,2]



Lymph Node

3. B-cell expansion[1,2,4,5]



2. Differentiates recruited immune cells into APCs[1,3]

APC=antigen presenting cell.

1. Seubert A, et al. *J Immumol.* 2008;180:5402-5412. **2.** Calabro S, et al. *Vaccine*. 2011;29:1812-1823. **3.** Schultze V, et al. *Vaccine*, 2008;26:3209-3222. **4.** Khurana S, et al. *Sci Transl Med.* 2010;2:1-8. **5.** Vono M, et al. *PNAS*. 2013;110:21095-21100.

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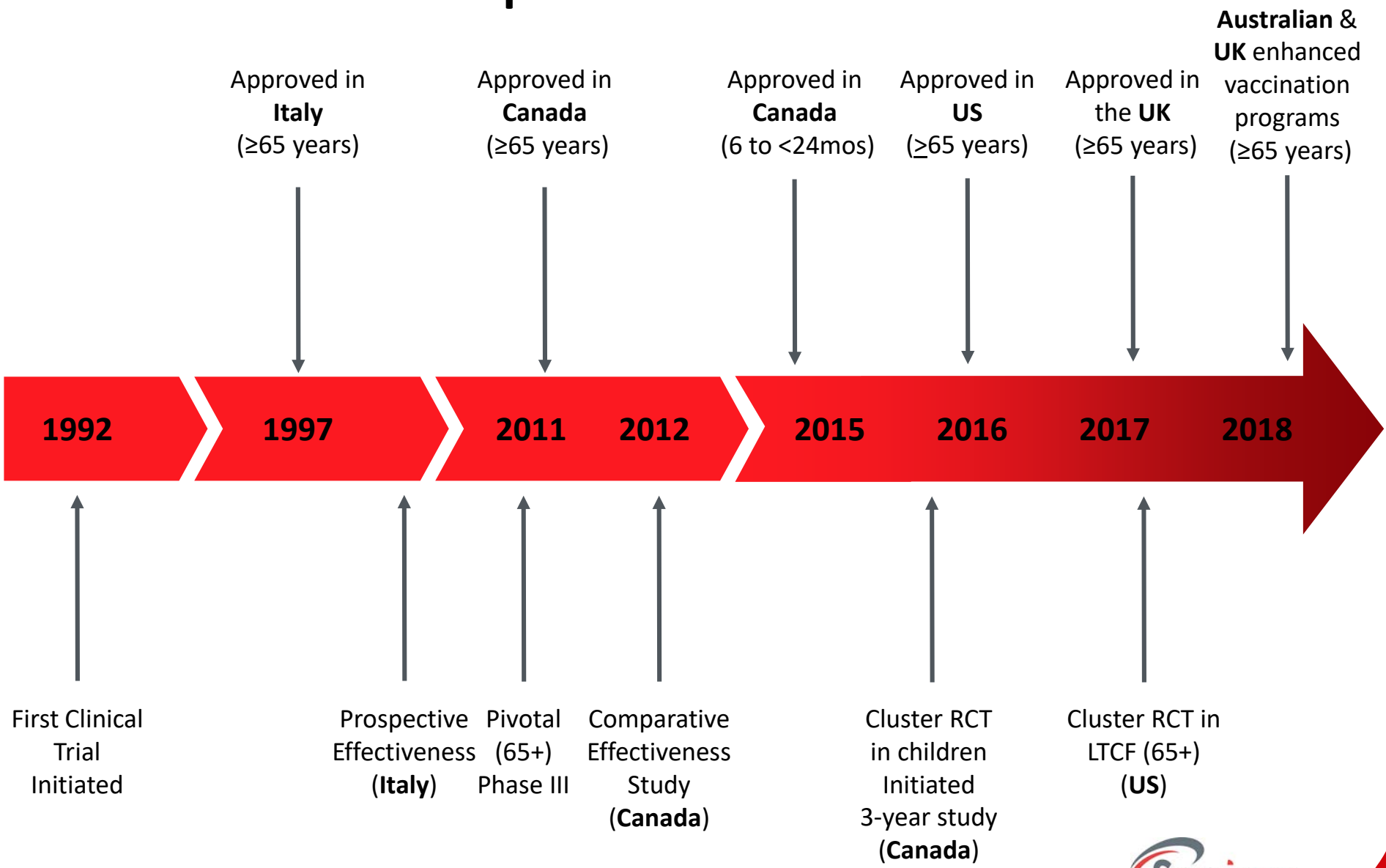
Timeline of Fluad Experience



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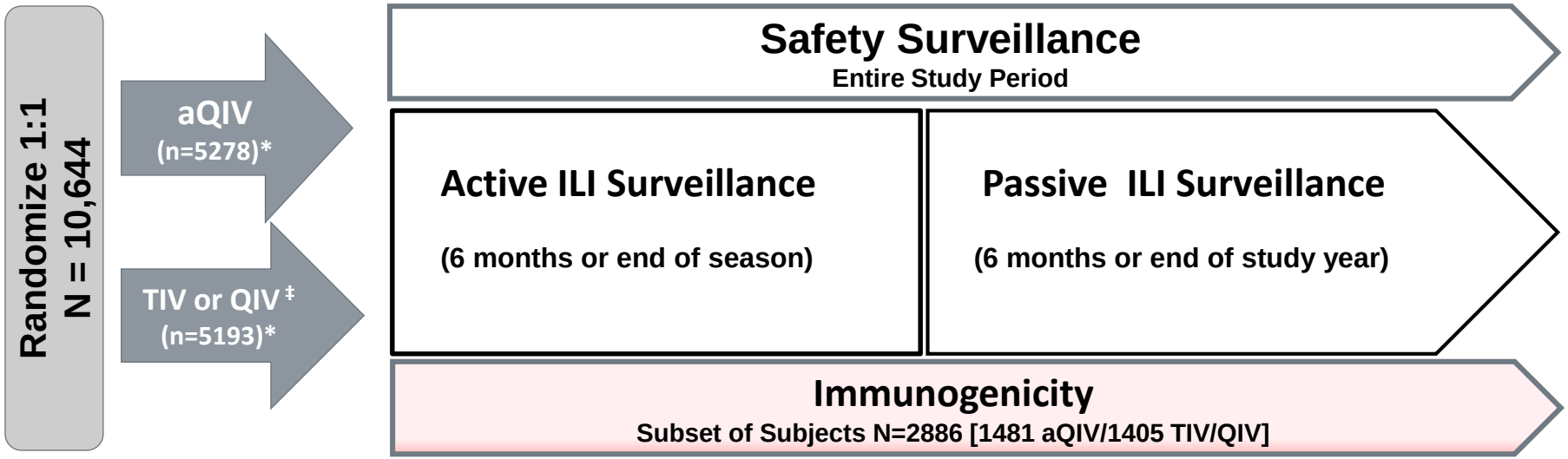
aQIV PIVOTAL STUDY IN YOUNG CHILDREN

aQIV, MF59-adjuvanted quadrivalent inactivated influenza vaccine

Fluad aQIV sBLA filed with FDA December 2017

Randomized Clinical Trial Design



ILI=influenza like illness; temperature of ≥100°F / ≥37.8°C along with any of the following: Cough, Sore Throat, Nasal Congestion, or Runny Nose in young children 6 months to 72 months

*Randomized subjects that were vaccinated and entered efficacy surveillance period ≥ 21 days after last vaccination

aQIV = adjuvanted quadrivalent inactivated influenza vaccine

‡ TIV/QIV=non-adjuvanted comparator vaccine (either trivalent influenza vaccine in Season 1 or quadrivalent influenza vaccine in Season 2)

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Baseline Demographics of Study Subjects

	Efficacy*		Immunogenicity†	
	aQIV n=5278 (%)	TIV/QIV‡ n=5193 (%)	aQIV n=1481 (%)	TIV/QIV‡ n=1405 (%)
Mean age, months	38.4 ± 18.43	38.0 ± 18.40	35.9 ± 18.58	35.3 ± 18.35
Age groups				
6 through 23 months	1299 (24.6)	1339 (25.8)	428 (28.9)	427 (30.4)
2 through 5 years**	3979 (75.4)	3854 (74.2)	1053 (71.1)	978 (69.6)
Dose groups				
0.25 mL	2484 (47.1)	2471 (47.6)	822 (55.5)	798 (56.8)
0.5 mL	2794 (52.9)	2722 (52.4)	659 (44.5)	607 (43.2)
Sex				
Male	2669 (50.6)	2652 (51.1)	734 (49.6)	708 (50.4)
Female	2609 (49.4)	2541 (48.9)	747 (50.4)	697 (49.6)

*Efficacy full analysis set comprised all participants who received study vaccine and provided efficacy data.

†Immunogenicity full analysis set included all subjects who received study vaccine and who provided at least one evaluable serum sample both before (baseline) and after vaccination.

‡Fluzone TIV in Season 1, Fluzone QIV in Season 2.

**Post-hoc analysis subgroup.

aQIV=adjuvanted quadrivalent inactivated influenza vaccine.

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Baseline Characteristics of Study

	Efficacy*			
	aQIV n=5278 (%)	TIV/QIV‡ n=5193 (%)		
Vaccine-naïve status**				
Naïve	**3553 (67.3)**	**3525 (67.9)**		
Non-naïve	**1725 (32.7)**	**1668 (32.1)**		
Season				
Season 1 (2013-14)	**757 (14.3)**	**699 (13.5)**		
Season 2 (2014-15)	**4521 (85.7)**	**4494 (86.5)**		
**********	**********	**********	**********	**********
Influenza strains	**A/H1N1**	**A/H3N2**	**B**	**B**
Season 1 Vaccine	**California**	**Texas**	**Brisbane**	**Mass**
Season 1 Circulating	**California**	**Texas**	**Brisbane**	**Mass**
Season 2 Vaccine	**California**	***Texas***	**Brisbane**	**Mass**
Season 2 Circulating	**California**	***Hong Kong***	**Brisbane**	**Mass**

*Efficacy full analysis set comprised all participants who received study vaccine and provided efficacy data.
‡ Fluzone TIV in Season 1, Fluzone QIV in Season 2.
**Vaccine-naïve=not received ≥2 doses of seasonal influenza vaccine since July 1, 2010, or who did not know their influenza vaccination history; vaccine-non-naïve=previously vaccinated and received ≥2 doses of seasonal influenza vaccine since July 1, 2010.
aQIV=adjuvanted quadrivalent inactivated influenza vaccine.

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Vaccine Efficacy: *PCR Confirmed Influenza Subjects 6 months to 72 months*

Strain, n (%)	aQIV n=5278 (%)	TIV/QIV* n=5193 (%)	rVE (95% CI)
No. Cases, Any strain	256 (4.9)	252 (4.9)	-0.67 (-19.81, 15.41)
A/H1N1	7 (0.1)	17 (0.3)	59.39 (2.06, 83.16)
A/H3N2	200 (3.8)	196 (3.8)	-1.33 (-23.41, 16.79)
B/Yamagata	36 (0.7)	36 (0.7)	2.09 (-55.44, 38.33)
B/Victoria†	14 (0.3)	9 (0.2)	-54.47 (-256.90, 33.14)

Primary Endpoint Success Criteria Defined as Lower 95% CI of rVE >0%

*Non-adjuvanted trivalent inactivated influenza vaccine (IIV3) in Season 1 and non-adjuvanted quadrivalent inactivated influenza vaccine (IIV4) in Season 2.
†B/Victoria cases from Season 1 have not been included in the analysis.

aQIV=adjuvanted quadrivalent inactivated influenza vaccine; CI=confidence interval; RT-PCR=reverse transcriptase polymerase chain reaction; rVE=relative vaccine efficacy.

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Vaccine Efficacy: *PCR Confirmed Influenza Subjects 6 months to 24 months*

Strain	aQIV (n=1299)	Fluzone TIV/QIV* (n=1339)	rVE (95% CI)
No. cases, Any strain	55	79	31.37 (3.14, 51.38)
A/H1N1	2	5	NA†
A/H3N2	44	66	34.50 (4.05, 55.28)
B/Yamagata	5	9	NA†
B/Victoria‡	4	0	NA†

Primary Endpoint Success Criteria Defined as Lower 95% CI of rVE >0%

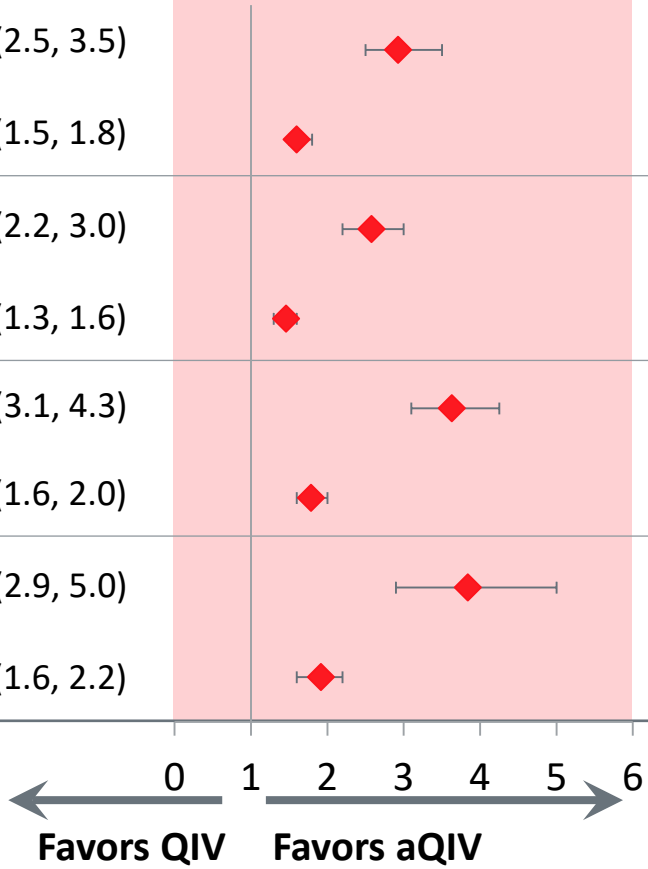
*Non-adjuvanted trivalent inactivated influenza vaccine (IIV3) in Season 1 and non-adjuvanted quadrivalent inactivated influenza vaccine (IIV4) in Season 2. †rVE was not calculated if number of cases was <20. ‡B/Victoria cases from Season 1 have not been included in the analysis.

aQIV=adjuvanted quadrivalent inactivated influenza vaccine; CI=confidence interval; NA=not applicable; rVE=relative vaccine efficacy.

Immunogenicity Results: GMTs & GMT Ratios

Subjects 6 months through 23 months and 2 through 5 years

		GMT		GMT Ratio (95% CI)	Superiority bound > 1	N	
		aQIV	Fluzone TIV/QIV			aQIV	Fluzone TIV/QIV
A/H1N1	**6-23 months**	654.99	223.88	**2.93** (2.5, 3.5)		378	384
	2-5 years	1110.84	692.98	1.60 (1.5, 1.8)		984	923
A/H3N2	**6-23 months**	982.98	380.79	**2.58** (2.2, 3.0)		378	384
	2-5 years	1261.91	862.17	1.46 (1.3, 1.6)		984	923
B/Yam-agata	**6-23 months**	130.25	35.89	**3.63** (3.1, 4.3)		378	384
	2-5 years	200.09	111.83	1.79 (1.6, 2.0)		984	923
B/ Victoria	**6-23 months**	292.45	76.07	**3.84** (2.9, 5.0)		167	179
	2-5 years	322.52	168.31	1.92 (1.6, 2.2)		578	559



Superiority defined as a lower boundary of the 95% CI >1. For B/Victoria results from Season 2 only are presented for both vaccine groups and used in the vaccine comparison analysis.

aQIV = adjuvanted quadrivalent inactivated influenza vaccine. CI = confidence interval. Comparator = non-adjuvanted comparator vaccine (either non-adjuvanted trivalent influenza vaccine in Season 1 or non-adjuvanted quadrivalent influenza vaccine in Season 2); FAS = full analysis set. GMT = geometric mean titer.

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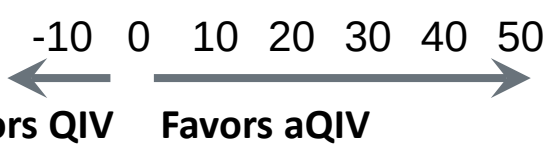
Immunogenicity Results: Seroconversion

Subjects 6 months through 23 months and 2 through 5 years

Homologous strains		Subjects with SC (%)		SC differences (95% CI)	Superiority bound > 0	N	
		aQIV	Comp			aQIV	Comp
A/H1N1	6-23 months	94.7	82.6	12.2 (7.8, 16.7)		378	384
	2-5 years	76.9	70.0	6.9 (3.0, 10.9)		984	923
A/H3N2	6-23 months	92.1	87.2	4.8 (0.5, 9.2)		378	384
	2-5 years	73.2	67.4	5.8 (1.7, 9.9)		984	923
B/Yam-agata	6-23months	84.9	50.5	34.4 (28.1, 40.4)		378	384
	2-5 years	86.5	70.6	15.8 (12.2, 19.5)		984	923
B/ Victoria	6-23 months	91.0	76.5	14.5 (6.9, 22.2)		167	179
	2-5 years	91.0	77.6	13.4 (9.2, 17.6)		578	559



Superiority defined as a lower boundary of the 95% CI >0. For B/Victoria results from Season 2 only are presented for both vaccine groups and used in the vaccine comparison analysis.

aQIV=MF59-adjuvanted quadrivalent influenza vaccine; CI=confidence interval; Comp=non-adjuvanted comparator vaccine (either non-adjuvanted trivalent influenza vaccine in Season 1 or non-adjuvanted quadrivalent influenza vaccine in Season 2).

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Solicited Local Adverse Events Reported
Through Day 7 After Any Vaccination

		6 to 24 Months		24 to 72 Months	
		aQIV N=1269	Comparator N=1308	aQIV N=3869	Comparator N=3748
Local Adverse Events		%	%	%	%
Tenderness	Any	26	21	49	38
	Severe	0.6	0.3	2	0.8
Erythema	Any (≥1 mm)	20	17	21	17
	>50 mm	0.2	0.1	1.2	0.7
Induration	Any (≥1 mm)	12	7	15	11
	>50 mm	0.1	0	0.7	0.3
Ecchymosis	Any (≥1 mm)	7	7	8	7
	>50 mm	0.1	0	0.03	0.03

Tenderness: moderate - cried or complained when touched; severe - cried when injected arm/leg was moved.

Solicited Systemic Adverse Events Reported
Through Day 7 After Any Vaccination

		6 to 24 Months		24 to 72 Months	
		aQIV N=1269	Comparator N=1308	aQIV N=3869	Comparator N=3748
Systemic Adverse Events		%	%	%	%
Irritability	Any	39	35	23	18
	Severe	1.7	1.6	1.2	0.5
Sleepiness	Any	30	28	25	19
	Severe	1.1	0.6	0.7	0.3
Change in eating habits	Any	27	25	21	15
	Severe	1.3	1.2	0.9	0.9
Diarrhea	Any	21	20	10	9
	Severe	1.5	1.2	0.4	0.3
Vomiting	Any	13	14	9	6
	Severe	0.8	0.2	0.2	0.3
Chills	Any	4	4	8	4
	Severe	0.2	0.2	0.2	0.1

Solicited Systemic Reactions (Fever) by Age Group 7 Days Following Any Vaccination

Following any vaccination		6 to 24 Months aQIV N=1269	6 to 24 Months Comparator N=1308	24 to 72 Months aQIV N=3869	24 to 72 Months Comparator N=3748
Fever[a]	Any	20%	14%	19%	9%
	≥39°C	5%	3%	4%	2%
	≥40°C	0.6%	0.3%	0.4%	0.3%

The majority of subjects with fever in both vaccine groups had fever <39°C.

Febrile convulsions observed during the treatment period were 2 subjects vs. 1 subject in the aQIV and comparator groups respectively

[a] Route overall (body temperature results are excluded if route of measurement is missing).
Fever was defined as body temperature ≥38°C by any route.

Co-vaccinations - Children with Fever Through Day 7 After Any Vaccination

Body Temperature (n)	≥6 to <24 Months aQIV N=21	≥6 to <24 Months Comparator N=22	≥6 to <72 Months aQIV N=26	≥6 to <72 Months Comparator N=29
≥38°C	3	1	4	3
≥38 - <39°C	1	0	2	2
≥39 - <40°C	2	1	2	1
≥40°C	0	0	0	0

[a] Route overall (body temperature results are excluded if route of measurement is missing).

Fever was defined as body temperature ≥38°C by any route.

Data on File

Unsolicited Adverse Events Reported After Any Vaccination

	6 to 24 months		24 to 72 months	
	aQIV N=1298	Comparator N=1328	aQIV N=3945	Comparator N=3833
	%	%	%	%
Any unsolicited AEs	**81**	**80**	**64**	**65**
Possibly or probably related unsolicited AEs	17	14	12	9
Any unsolicited SAEs	7	6	4	4
Possibly or probably related unsolicited SAEs	0.2	0.1	0.1	0
Any unsolicited AEs leading to death	0	0	0.03	0.1
Any unsolicited AEs leading to premature withdrawal	0.2	0.1	0.2	0.2
Any unsolicited AEs leading to hospitalization	6	6	3	3
Any unsolicited AEs leading to NOCD	2.4	1.7	1.4	1.9
Any unsolicited AESI	0.2	0	0.1	0.1

AE-Adverse Event; SAE-Serious Adverse Event; NOCD-New Onset Chronic Disease; AESI-Adverse Events of Special Interest

Safety Summary

- Increased incidence of local and systemic reactogenicity is seen after vaccination with aQIV, consistent with past pediatric aTIV trials
- The majority of local and systemic AEs started within the first 3 days after vaccination, were mild to moderate in severity and observed up to a total of 2 to 3 days
- Increased incidence of fever compared to comparator vaccines, no increase in febrile convulsions
- Comparable incidences of unsolicited AEs, AESIs, and NOCDs

Efficacy and Immunogenicity Summary

- Efficacy and Immunogenicity: 6-72 months
  - aQIV efficacy was comparable to the comparator for PCR confirmed influenza*
  - aQIV elicited a superior immune response as reflected by GMT ratios relative to the comparator vaccine against all 4 strains
- Efficacy and Immunogenicity: 6-24 months
  - aQIV efficacy was significantly greater for PCR confirmed influenza
  - aQIV elicited a superior immune response as reflected by GMT ratios relative to the comparator vaccine against all 4 strains

*Primary endpoint of superior rVE for prevention of RT-PCR confirmed influenza was not met.

aQIV=adjuvanted quadrivalent inactivated influenza vaccine; RT-PCR=reverse transcriptase polymerase chain reaction; rVE=relative vaccine efficacy.